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(54) Pharmaceutical composition for implantation

(57) The present Invention relates to a pharmaceutical composition for implantation in a natural, pathological or artificial cavity in body tissue. The composition comprises $CaSO_4$ (e.g. as gypsum or plaster of Paris), and at least one antibiotic substance selected for its ability to be slowly released from the $CaSO_4$ and to maintain antibiotically effective concentrations in fluid in the cavity for a period of up to several weeks.

The preparation of the composition comprises mixing plaster of Paris (calcium sulphate, hemihydrate) with the desired antibiotic substance or substances and water, optionally adding auxiliary agent(s) and allow the slurry obtained to set in moulds, or *in situ*. The antibiotic is fusidic acid and/or gentomycin.

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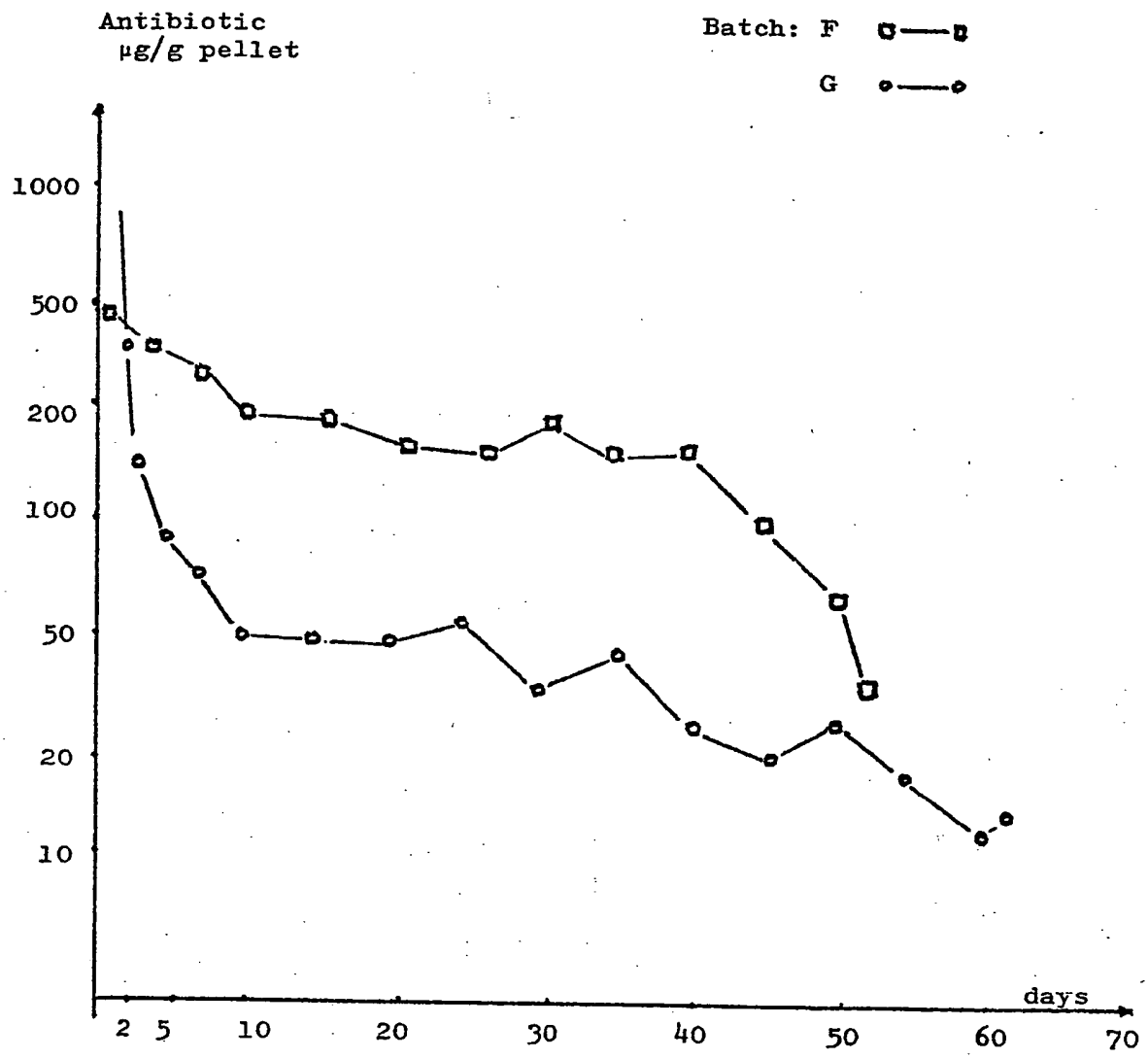
Release of antibiotic in vitro



SPECIFICATION

Pharmaceutical composition for implantation

This invention relates to a pharmaceutical composition for implantation in a natural, pathological or artificial cavity in body tissue of animals, including humans, its preparation, its form of presentation and its use.

It is known that calcium sulphate, hereinafter referred to as gypsum or plaster of Paris, is when set an effective filler of bone cavities in cases of osteomyelitis and bone cysts, and that it is spontaneously absorbed over a period of some months, being replaced by bone of normal architecture. In the absence of a filler, such cavities tend to be occupied by haematomata or blood clots, which likewise disappear slowly giving way to new bone tissue, but which during their residence in the cavities constitute a haven and a growth medium for microorganisms including pathogenic and pyogenic bacteria. It is also the case that gypsum fillers, without additives, have no particular effect in discouraging bacterial infection apart from the mechanical exclusion of clots.

It is known likewise to fill bone cavities with beads or the like composed of synthetic resin cement and impregnated with at least one antibiotic substance which diffuses into the cavities over a prolonged period, this being an effective local antibiotic, therapeutic or prophylactic, method of treatment. These beads, which are conventionally strung together on an insert metal wire in the manner of a necklace or chaplet, are not however absorbed by the human body and it is generally thought proper to remove them, a few at a time, in subsequent surgical operations which have no other purpose. These operations have the disadvantageous side-effect of reopening relatively fresh wounds, of disturbing replacement tissue which may have begun to surround some or all of the beads, and of involving a risk of re-infection, or re-activation of old infection sites. Removal of beads leaves dead spaces which it is customary to refill with autogenous cancellous bone graft; this is a further complication of the method.

Among the objects of the invention are the alleviation or removal of some or all of the above recited disadvantages.

It has been found that certain antibiotic substances when present in admixture with small bodies of gypsum, and exposed to fluids, e.g. water, buffer solutions or body fluids, are released from said bodies to appear in said fluids, the rate of release being dependent on several conditions, e.g. the choice of antibiotic, the preparation of said bodies and other factors. This phenomenon permits a therapeutically or prophylactically effective concentration of antibiotic substances to be maintained for that period in an environment of which the volume is suitably limited, as for example the volume of a cavity in a body tissue such as bone is limited. The period in question

It is, however, important that the release of the antibiotic substance has an optimal rate being neither too fast nor too slow, and it has now surprisingly been found that, in particular, the antibiotics fusidic acid and gentamycin and salts thereof each and together fulfill the desired releasing requirements giving rise to both a favourable prolonged and adequate antibiotic activity in the fluids of the cavities. For the easy reference it shall be emphasized that fucidin is the trade name for fusidic acid or its salts.

The invention therefore provides a pharmaceutical composition adapted for implantation in a natural, pathological or artificial cavity in a body tissue, which composition comprises $CaSO_4$ with from 1/2 to 2 mol H_2O and at least one antibiotic substance selected from the group consisting of fusidic acid and/or gentamycin or salts thereof, optionally combined with other antibacterial substances, said composition selected for its ability to be slowly released from gypsum and to maintain antibiotically effective concentrations in fluids in the cavity.

Fusidic acid and gentamycin or salts thereof have according to experiments shown a surprising suitable degree of release from the gypsum. They can in some cases with advantage be supplemented with another antibacterial substance which then are mixed together in a suitable ratio in the composition in order to obtain a broader antibacterial spectrum of the composition. Such other antibacterial substances may be e.g. sulfonamides, or antibiotics, e.g. β-lactam antibiotics such as ampicillin, cloxacillin, oxacillin, or pro-drugs thereof, optionally together by β-lactamase inhibitors, or rifampicin, erythromycin, or cephalosporins. It can, in particular, be advantageous to mix fusidic acid or its salts with aminoglycoside, as e.g. gentamycin or salts thereof. In such cases the releasing rate of each of the components will have to be taken into consideration to secure that the concentration in the body fluids will be optimal. This can be achieved e.g. by addition of suitable auxiliary agents, which are able to influence the setting time, the structure of the gypsum and thereby the releasing rate of the antibiotics, or by coating the antibiotic in question in known manner in order to obtain substantially same releasing rate of the antibiotics used.

As a further advantage by using the said antibiotics can be mentioned that fusidic acid is known for its ability to promote wound-healing and gentamycin is known for its particular suitability for treatment and prophylaxis in the management of bone conditions.

It will be appreciated that the invention is not restricted to compositions for bone implantation. There seems no reasons why cavities in tissues other than bone should not respond well to implantation with the invention compositions.

The composition of the invention can be presented in several forms and sizes. It is, however, preferred that the composition should be

pellets being implanted so as substantially to fill a cavity in a tissue under treatment. However other forms such as beads or flakes, pills or tablets, or a powder for preparation of larger casting *in situ* designed to occupy a substantial part of all of the volume of a given cavity, comprise possible embodiments within the scope of the invention.

The pellets, beads, etc. are preferably cast from an aqueous slurry of unset gypsum, i.e. calcium sulphate hemihydrate, also called plaster of Paris, a predetermined proportion of the selected antibiotic substance or substances being mixed, either into the aqueous part or the gypsum part of the composition, if desired together with auxiliary agents capable of influencing the setting time. A pretreatment of the antibiotic, e.g. by microencapsulation in a suitable medium known in the pharmaceutical technique can control or sustain the release from the resulting composition during its presence in the cavity.

The slurry is filled into suitable moulds and allowed to set. The resulting pellets, beads or the like are removed from the moulds, dried and packaged. Alternatively, a dry mix of unset gypsum and antibiotic, containing conventional tabletting excipients, may be compounded and formed into suitable bodies, granulates or powders by standard pharmaceutical techniques. Such compositions absorb water from body fluids after implantation, and set *in situ*. It shall, however, be noticed that this absorption gives rise to evolution of heat, and certain precautions therefore have to be taken by this method, e.g. by addition of setting inhibitors such as colloids. A third method of manufacture starts from set gypsum (dihydrate) in powdered form, to which antibiotics and tabletting excipients are added, and the mixture compounded as before, and compressed into pellets, bead or the like. This product, consisting substantially of set gypsum, does not undergo the process of setting after implantation but behaves similarly to the cast pellets etc. previously referred to.

By addition of auxiliary agents the setting time can either be retarded, e.g. by adding a colloid, such as dextran, or other blood-plasma substituents, or any substance which will decrease the solubility of the gypsum, such as ethanol, or can be accelerated by e.g. adding sodium chloride, potassium sulphate or other salts, thereby also influencing the releasing rate in an advantageous manner.

Adjuvant substances for various purposes may be incorporated in the composition of the invention, e.g. X-ray contrast media.

The antibacterial substances can be used either as such, or in the form of suitable salts depending on their different solubilities, pH-values, stabilities and other factors influencing the preparation of the pellets, beads, etc.

Such salts can be alkali-metal salts or organic salts, e.g. with diethanolamine, of fusidic acid and the hydrohalides, the sulphate etc. of gentamycin.

The composition of the invention is preferably presented in a clinically sterile form, and is advantageously presented in a sterile package for convenience in use. The beads, pellets, flakes or castings may be manufactured under sterile or aseptic conditions from sterile ingredients, or the finished, packed product may be sterilised by exposure to ionizing radiation or other suitable known technique.

Since the invented composition is spontaneously absorbed by the body, the pellets or beads do not need to be threaded on an inert wire for accessibility.

The amount of antibiotic substance in the implantation units has to be of a range which gives rise to a therapeutically acceptable concentration of the antibiotic in the cavity fluids during the treatment period. The number of units used depend on the circumstances, e.g. the size of the cavity or the size of the units, many small pellets giving faster release of the antibiotic. For different purposes therefore different amounts of antibiotic in the pellet will be used, but will for most purposes be within the range of from 50 mg to 1000 mg per 10 g of gypsum, preferably from 100 to 500 mg per 10 g. In the case where two antibiotics are used they are advantageously mixed in a ratio of from 10:1 to 1:10, preferably of from 3:1 to 1:3.

When fusidic acid or salt thereof is used alone an amount of from 200—300 mg per 10 g gypsum is advantageous.

Pellets prepared as described in the example 1 where tested to determined the rate at which they released the contained antibiotic in an environment roughly simulating the conditions to which they would be subject following implantation. Two batches of pellets were chosen, prepared each time from 10 g plaster of Paris containing respectively 250 mg fusidic acid and 500 mg gentamycin. The batches, labelled F and G comprised pellets containing respectively 2.9 mg and 5.75 mg of the respective antibiotic per pellet.

For each test, 10 pellets were taken from a selected batch and placed in 20 ml buffer solution in a large test tube, which was then incubated at 37°C for 24 hours. The buffer solution was then carefully removed and stored at —20°C pending assay. The pellets were washed twice with fresh buffer solution which was discarded. A second 20 ml portion of buffer solution was added to the pellets in a similar test tube which was incubated for a further 24 hours at 37°C, the buffer solution being then removed as before and stored at —20°C to provide the second sample for assay This procedure was repeated daily, yielding a sample every day, until the series of tests was deemed complete (see below) or the pellets began to disintegrate. Several tests of this kind were performed simultaneously on each of the two batches.

As a running check on the progress of the tests, each separated portion of buffer solution, following its removal from the pellets, and prior to storing at —20°C, was checked for the presence of antibacterial activity by placing one drop thereof

on a standard agar plate inoculated with a strain of Micrococcus pyogenes *var.* aureus (Staphylococcus aureus) which was sensitive to the respective antibiotic. The plate was then incubated at 37°C for 24 hours and inspected for signs of a circle of inhibition indicating antibacterial activity. When, in the course of each series of tests of a particular set of 10 pellets, activity was first shown to be absent, the series was deemed complete and no further tests were carried out.

The frozen samples of buffer solutions, which samples had been carefully labelled as to batch, series number and date, were then thawed out and assayed, each for its respective antibiotic substance. This was done by the agar diffusion test, as modified after Grove and Randell (1955), using the paper disc method. For batch G, the test organism used was Bacillus subtilis ATCC 6633, and Difco medium No. 1. For batch F the test organism was a local hospital strain of Staphylococcus aureus, on Difco medium No. 5.

The results, which are set out in graphic form in the accompanying drawings, are calculated in terms of micrograms of antibiotic released per grame of pellet material exposed to 20 ml of buffer solution for 24 hours. They should be divided by 5 for micrograms per pellet released daily under the same conditions, and the latter figure divided by 20 to obtain the daily release rate in micrograms per tablet per ml of fluid in a closed cavity with a volume of 20 ml.

The following observations are included to amplify the results summarized in the drawing.

Fusidic acid (250 mg/10 g plater) is slowly liberated at significant levels until the pellet finally disintegrates. Initially 450—500 μg/g pellet/day are released, a rate which finally falls to 50 μg/g original pellet by day 50.

Gentamycin pellets 500 mg/10 g plaster) release 41 mg/g pellet (approximately 80% of the contained antibiotic) in the first 24 hours. By the fifth day, this high level has fallen to 50 μg/g pellet/day, and thereafter there is a slow progressive decay until a final level of 12μg/g original pellet is reached at the time of disintegration of the pellet. Pellets containing 250 mg gentamycin/10 g plaster liberate 15.8 mg (approximately 60%) gentamycin/g plaster in the first day, 25 μg by day 15, and release thereafter, rapidly falls to trace amounts.

Control pellets containing no antibiotic showed no antibacterial action.

The binding capacity of the pellets is obviously different for the two antibiotics. The plaster of Paris slurry used to make the pellets is slightly acid (pH 6). The fact that fusidic acid crystallised at this pH might explain its slower release until final disintegration of the pellets. Gentamycin is soluble at pH 6, and diffuses initially more rapidly, though release persists until final disintegration.

For the purpose of protracted release, fucidin and gentamycin are obviously excellent. The Minimal Inhibitory Concentration (M.I.C.) of fucidin for sensitive Staphylococcus aureus lies in the range 0.10—0.32 μg/ml. The M.I.C. for sensitive organisms with gentamycin, in μg/ml, for Staphylococcus aureus is 0.5, for Escherichia coli 1—4, for Proteus 1—12, for Pseudomonas 1.5—12. Thus for fucidin and gentamycin, the rate of release is such, that if the pellets are contained within a cavity and the organism is sensitive, the concentration of antibiotic should be well in excess of the M.I.C.

Theoretically, toxic levels of gentamycin could be reached in the first day is more than 20—30 gentamycin pellets of the strength here considered were implanted in an adult patient. *In vivo* experiments indicate that the danger is more theoretical than real. However, it may provide necessary, as part of the preparation of the gentamycin pellet for implantation, to place it in an eluant fluid for up to 24 hours. This simple measure would effectively reduce serum levels to trace amounts, as the pellets release only 300—400 μg gentamycin/g pellet on day 2.

By contrast, fucidin is liberated at a more steady rate, even from day 1, and thus toxicity should not prove a problem.

It is also within the scope of the invention that, if indicated, fucidin pellets and pellets with gentamycin or another antibiotic and antibacterial substance could be used simultaneously in the same implantation. The user is thereby free to choose and vary the amount and ratios of antibiotics in accordance with the character and degree of the infection of the patient.

Clinical reports show very successful results of the treatment with antibiotic loaded gypsum pellets (ALGP) according to the invention. Of 13 patients treated with ALGP complete healing was seen in 11 cases without complications. Even where a great number of pellets were implanted the serum calcium did rise above normal, but rose in one case from abnormal low to normal in a few weeks.

The invention is not limited by or to the details of the specific embodiments described, many of which can undergo wide variation without departing from the scope of the invention.

The invention is set out in greater detail in the following example.

EXAMPLE

100 g commercial grade gypsum plaster, $CaSO_4 \cdot 2H_2O$ was dried to constant weight in a hot air oven at 100°C for 4 hours and allowed to cool. The cooled material was subdivided into portions each weighing 10 g, and these portions were sterilised in a hot air oven at 160°C for 4 hours.

Pellets were prepared under bacteriologically sterile conditions as set out hereunder. The temperature of the materials used was first lowered to 0°C to delay the setting time of the gypsum.

To each 10 g portion of gypsum a quantity of either 250 mg or 500 mg of the relevant antibiotic, or antibiotics, corrected to give said amounts of the pure substance by reference to the manufacturer's

index of purity, was added and thoroughly mixed in. A measured volume of sterile physiological saline (5—7 ml) was added to the mixture to give a slurry of optimum consistency for handling. The exact volume of saline was previously determined empirically. The slurry was taken up into a sterile syringe, dispensed therefrom into previously sterilised moulds, and allowed to set. The resulting pellets were removed from the moulds, and stored at 0°C.

This procedure yielded, for each 10 g portion of gypsum, about 80 flat cylindrical pellets weighing 0.18 to 0.20 g each being of diameter 6 mm and height 4 mm. The pellets were packaged under aseptic conditions in heat-sealed sachets of transparent plastics material previously sterilised, 200 pellets to a sachet.

Each pellet accordingly contained 5.75 mg or 2.9 mg of pure antibiotic, according to whether 500 mg or 250 mg thereof has been added to the 10 g portion of gypsum. The product was now ready for use in surgical implantation.

CLAIMS

1. A pharmaceutical composition adapted for implantation in a natural, pathological, or artificial cavity in a body tissue, which composition comprises $CaSO_4$ with from 1/2 to 2 ml H_2O and at least fusidic acid and/or gentamycin or salts thereof, optionally combined with other antibacterial substances.

2. A pharmaceutical composition according to claim 1 in which is used gypsum.

3. A pharmaceutical composition according to claim 1 in which is used plaster of Paris.

4. A pharmaceutical composition according to claims 2 and 3 in which the antibiotic substance is fusidic acid or a salt thereof.

5. A pharmaceutical composition according to claims 2 and 3 in which the antibiotic substance is a mixture of fusidic acid or salt thereof and gentamycin or a salt thereof.

6. A pharmaceutical composition according to claim 5 in which fusidic acid and gentamycin is used in a ratio of from 10:1 to 1:10.

7. A pharmaceutical composition according to claim 5 in which fusidic acid and gentamycin are present in ratio of from 3:1 to 1:3.

8. A composition as claimed in claims 1 to 7 in form of pellets, tablets, beads, pills or premanufactured units produced by setting the plaster of Paris in any suitable form adapted for implantation.

9. A composition as claimed in claim 1 to 7 in form of powder, flakes or granules.

10. A pharmaceutical composition according to any of the foregoing claims containing from 50 mg to 1000 mg of fusidic acid and its salts per 10 g gypsum.

11. A pharmaceutical composition according to any of the foregoing claims 1—9 containing from 100—500 mg fusidic acid and its salts per 10 g gypsum.

12. A pharmaceutical composition according to claims 8 and 9 in which the total amount of antibiotic substances is from 50—1000 mg per 10 g of gypsum.

13. A pharmaceutical composition according to claim 8 and 9 containing 200—300 mg of fusidic acid or a salt thereof per 10 g gypsum.

14. A pharmaceutical composition according to claims 8 and 9 containing from 50 mg to 1000 mg of gentamycin or a salt thereof per 10 g gypsum.

15. A pharmaceutical composition according to claim 14 containing 100—500 mg gentamycin or a salt thereof per 10 g of gypsum.

16. A composition in any of the foregoing claims which contain as further ingredient or ingredients known pharmaceutically acceptable auxiliary agents affecting the setting time of plaster of Paris, as well as the releasing time, or X-ray contrast media.

17. A method for the preparation of a pharmaceutical composition according to claim 1 comprising mixing plaster of Paris (calcium sulphate, hemihydrate) with the ingredients, reacting the mixture with sterile water for injection and allow the slurry obtained to set in moulds of the desired form and size.

18. A method for the preparation of a pharmaceutical composition according to claim 1 comprising mixing plaster of Paris (calcium sulphate, hemihydrate) with a sterile mixture of water and the antibiotic substance or substances and allow the slurry obtained to set in moulds of the desired form and size.

19. A method for the preparation of a pharmaceutical composition according to claim 1 comprising mixing powdered, set gypsum with the antibiotic material and, if desired, the auxiliary agents to a powder and optionally by standard pharmaceutical technique compound and transform the powder to granules, flakes, pills, tablets, pellets and beads.

20. A method as claimed in claim 17—19 in which the ingredients are sterile and the procedure aseptic.

21. A method as claimed in claim 17—19, followed by sterilisation of the resulting product.

22. For implantation in a natural, pathological, or artificial cavity in the body the use of the composition of claim 1.

23. In the use as claimed in claim 22 the simultaneous use of compositions as claimed in claim 1, each of them containing different antibiotics.

24. In the use as claimed in claims 22 to 23, the use of a composition in which the setting takes place *in situ*.

25. A pharmaceutical composition adapted for implantation in a natural, pathological or artificial cavity in body tissue substantially as hereinbefore

described in the foregoing Example.

26. A method for the preparation of a pharmaceutical composition adapted for implantation in a natural, pathological or artificial cavity in body tissue substantially as hereinbefore described in the foregoing Example.

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